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Exercise-Induced ST Segment Elevation in a Patient With Effort Angina Pectoris and Normal Coronary Arteries

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A 32 year old woman who complained of exercise-induced chest pain was found to have widespread elevation of the ST segment of the electrocardiogram during exercise testing. Coronary angiography demonstrated no obstructive lesions and no evidence of coronary artery spasm despite ergonovine administration, bicycle ergometry and rapid atrial pacing. Exercise thallium-201 scintigraphy demonstrated no perfusion defects despite ST segment elevation. Radionuclide blood pool imaging revealed a slight decrease in ejection fraction with exercise. The available evidence raises the possibility of small vessel coronary artery disease, either structural or vasotonic, as a cause of this patient's symptoms.

Exercise-induced elevation of the ST segment of the electrocardiogram in patients without recent myocardial infarction or ventricular aneurysm is generally thought to represent transmural ischemia due to severe atherosclerotic coronary artery disease or coronary artery spasm with or without underlying coronary artery disease. In previously reported cases (1–4) it has been associated with a defect in thallium-201 perfusion scanning. In addition, coronary artery spasm during exercise has been demonstrated with coronary angiography in some of these cases (2,5,6). This report describes a patient with exercise-induced chest pain and ST elevation without a concomitant thallium perfusion defect and no evidence of coronary artery spasm at angiography.

Case Report

Clinical history. The patient is a 32 year old white woman referred to North Carolina Memorial Hospital for cardiac catheterization for evaluation of chest pain and an abnormal exercise tolerance test. She first noted chest pain with exertion as a child. She was unable to undertake gym classes in elementary school due to chest pain. Evaluation by her family physician and an orthopedist identified no abnormalities at that time.

The complaints have continued into adult life. She experiences severe, heavy substernal chest pain occurring with varying amounts of activity several times per week. The pain is always relieved by rest; she has never used nitroglycerin for the pain. She has smoked 1½ packs of cigarettes per day for 15 years. There is no history of rheumatic fever, heart murmur or hypertension. Her family history is negative for heart disease. She takes no medications. Her referring physician performed an exercise tolerance test that revealed ST segment elevation induced by exercise and she was referred for cardiac catheterization.

Exercise testing. Her physical examination was entirely unremarkable. A chest roentgenogram, blood chemistry values, urinalysis and complete blood count were normal. There was no evidence of collagen vascular disease. The electrocardiogram revealed poor R wave progression in the precordial leads and T wave inversion in the inferior leads and V_4 through V_6 (Fig. 1). The patient underwent a graded exercise tolerance test using the standard Bruce protocol. At 3 minutes into exercise, she developed chest pain at a heart rate of 160 beats/min. At the next minute of exercise, she developed 1 to 4 mm of ST elevation in leads I, aVL and V_3 through V_6 (Fig. 1). The electrocardiographic changes and chest pain resolved within 1 ½ minutes of stopping the test.

Coronary angiography during ergonovine testing, exercise and rapid atrial pacing. Cardiac catheterization was performed using the Judkins technique. Right- and left-sided intracardiac pressures were normal and there was no evidence of valvular disease. The left ventriculogram demonstrated normal wall motion. All branches of the left and

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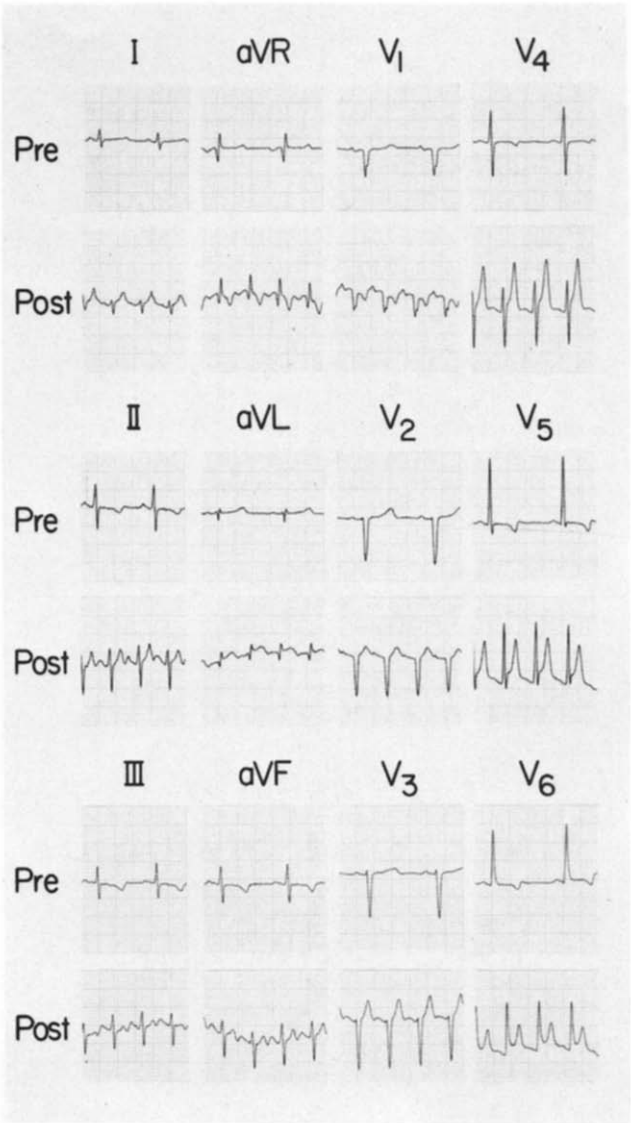

Figure 1. Rest electrocardiogram before exercise (Pre) illustrating poor R wave progression in the precordial leads and T wave inversion in V_4 through V_6. Below each lead is the immediately post-exercise electrocardiogram (Post) demonstrating marked ST segment elevation in leads I, aVL and V_3 through V_6.

right coronary arteries were visualized in multiple projections including axial views, and there were no obstructive lesions.

Progressive supine bicycle ergometry during the catheterization was performed to 100 Ws. The patient became fatigued at a heart rate of only 125 beats/min but had no chest pain; there were no electrocardiographic changes. A total of 0.55 mg of ergonovine was then administered in divided incremental doses. The patient experienced no chest pain and there were no electrocardiographic changes. Angiograms of both the left and right coronary arteries immediately after ergonovine administration revealed mild diffuse narrowing, but no focal coronary spasm (Fig. 2). Rapid atrial pacing was performed to a rate of 165 beats/min, at which point the patient complained of severe chest pain identical to her usual pain. There were no electrocardiographic changes at this time and angiograms of both right and left coronary systems again revealed no evidence of coronary spasm.

Thallium stress testing. After recovery from the catheterization, the patient underwent a thallium-201 exercise test. She exercised for 5 minutes on an upright bicycle ergometer and again experienced chest pain and ST elevation in leads I, aVL and V_3 through V_6 at a heart rate of 187 beats/min. There was no evidence of a perfusion defect at maximal exercise. Comparison of the stress images to subsequent rest images obtained 4 hours later revealed normal thallium distribution. Twenty-four hours of Holter monitoring revealed no episodes of ST segment shift.

Therapy and follow-up. The patient was lost to follow-up for 4 months, but on return to the hospital she underwent a repeat exercise tolerance test that again produced chest pain and ST elevation at the same heart rate. Therapy was begun with nifedipine, 30 mg 3 times daily, and during 2 weeks of therapy, she experienced no amelioration of symptoms of chest pain. An exercise tolerance test again showed ST elevation in the same leads at a heart rate of 160 beats/min.

Nifedipine was discontinued and therapy was begun with propranolol, 60 mg 4 times daily. Repeat exercise testing resulted in no chest pain and only 0.5 mm of ST elevation in leads V_5 and V_6 at a heart rate of 130/min after 5 minutes of exercise. She has continued on propranolol therapy for 18 months with only occasional episodes of exercise-induced chest pain.

One year after initiation of propranolol therapy, the patient underwent rest and stress first pass and multigated equilibrium radionuclide angiography after withholding medication for 2 weeks. The first pass ventricular angiogram revealed normal wall motion and an end-diastolic volume index of 81 cc/m^2 and an end-systolic volume index of 30 cc/m^2 at rest. Supine bicycle ergometry was performed and a heart rate of 168 beats/min and a systolic blood pressure of 185 mm Hg were achieved. The patient experienced chest pain, and although there was no ST elevation, the T waves in the monitored V_5 lead became tall and peaked. An end-diastolic and end-systolic volume index of 84 and 33 cc/m^2, respectively, were recorded. The ejection fraction at rest by the gated equilibrium technique was 63% with normal wall motion. Supine bicycle ergometry was again performed and a heart rate of 157 beats/min and a systolic blood pressure of 160 mm Hg were obtained. She again developed chest pain and the T waves in lead V_5 became peaked, but there was no ST segment elevation. The ejection fraction obtained during exercise was 61%. In both studies, the stress radionuclide ventriculogram revealed no focal wall motion abnormality.

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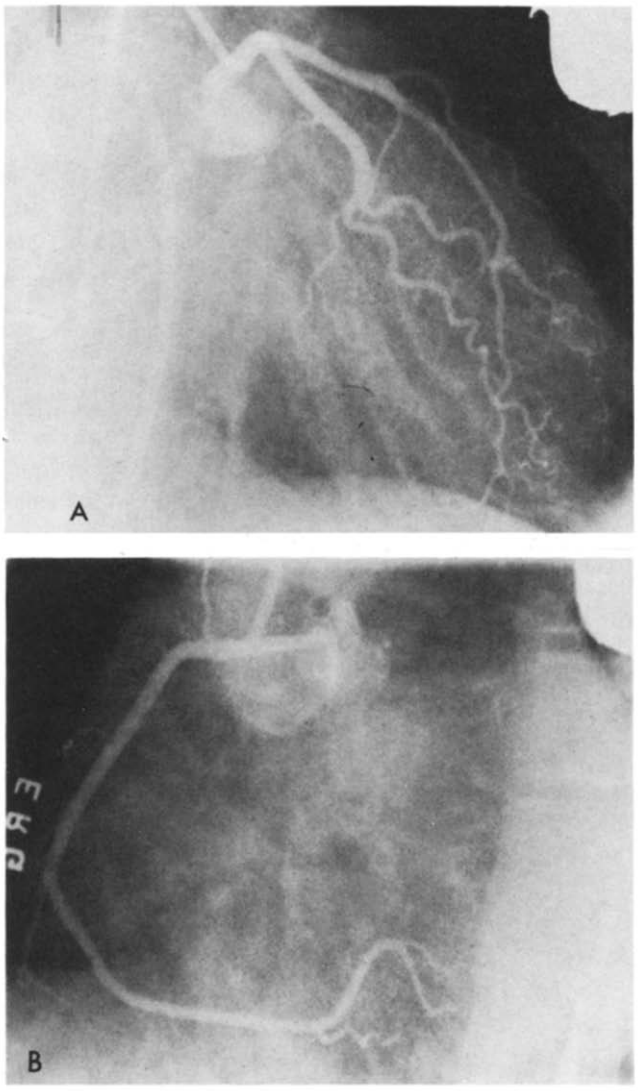

Figure 2. A, Right anterior oblique angiogram of the left main, left anterior descending and circumflex coronary arteries. **B,** Left anterior oblique angiogram of right coronary artery. These angiograms, taken after administration of ergonovine, show mild diffuse narrowing, but no evidence of focal coronary artery spasm.

Discussion

Reversible ST segment elevation during exercise testing may occur at the site of a ventricular aneurysm or a previous myocardial infarction (3,5,7). In the absence of these conditions, exercise-induced ST elevation has been thought to be due to ischemia caused by a severe atherosclerotic lesion in the vessel supplying the ischemic area, with or without superimposed spasm, or by spasm in an otherwise normal coronary artery (1,3,6,8).

Exercise-induced ST elevation caused by coronary spasm. Of 82 patients with previously diagnosed variant angina in one study (9), 30% were found to have ST segment elevation on exercise testing. Regardless of the severity of underlying occlusive disease, patients with exercise-induced ST elevation uniformly exhibit a marked tendency to develop coronary spasm on exercise testing or ergonovine administration during coronary angiography (2,6,9,10). Exercise testing with thallium-201 scintigraphy in such patients has invariably shown reversible perfusion defects suggesting transmural ischemia (3,7,11). Pfisterer et al. (12) reported a patient who demonstrated reversible thallium perfusion defects and ST elevation with ergonovine administration, but no angiographically demonstrable atherosclerotic disease and no spasm of visible epicardial arteries. Yasue et al. (6) reported a circadian rhythm of exercise-induced ST elevation; however, Specchia et al. (2) were unable to confirm this finding. The presence of ST elevation during exercise testing in patients with variant angina appears to correlate with the degree of clinical activity of the disease (9). Patients with exercise-induced coronary spasm have generally responded to treatment with calcium channel blockers while showing little or no response to beta-receptor blockers (9,10,13).

Exercise-induced ST elevation in the absence of coronary spasm. Our patient has demonstrated clear-cut ST elevation and chest pain, both reproduced on numerous occasions over prolonged observation at various times of the day, and without correlation with any clinical variables. The ST elevation could not be related to coronary spasm during coronary angiography nor to regional ischemia during thallium stress testing. The response to beta-receptor blockers and lack of response to calcium channel blockers is atypical for classic coronary artery spasm. Furthermore, the history of chest pain occurring since childhood has not been reported, to our knowledge, in coronary artery spasm.

Pathophysiologic mechanisms. The exact pathophysiology of this patient's syndrome remains unknown. One possible explanation is that this pattern represents a false positive exercise electrocardiogram and the patient really has no cardiac disease. Alternatively, she could truly have coronary artery spasm and the response to ergonovine administration and thallium perfusion exercise testing may have been false negative. Our belief is that she has some diffuse structural or vasotonic abnormality of the small coronary vessels.

It is possible that this patient represents an unusual form of the poorly defined syndrome X (14). This syndrome is associated with exertional chest pain, evidence of abnormal myocardial lactate metabolism, normal coronary angiograms and abnormal mitochondrial structure on myocardial biopsy (15,16). Many patients with this syndrome have an abnormal electrocardiographic stress test, but we are unaware of any cases of ST segment elevation associated with this syndrome. Syndrome X is poorly defined and many patients thought to exhibit this syndrome were studied before the advent of ergonovine testing and the increased awareness

of coronary artery spasm. If our patient has syndrome X, the ST segment elevation would make this case quite unusual.

It is also possible that this case represents small vessel spasm of the type proposed by Pfisterer et al. (12). We were unable to demonstrate thallium perfusion defects during an episode of exercise-induced chest pain and ST elevation, whereas the case that Pfisterer et al. reported did show such a defect. Nonquantitative thallium-201 perfusion scintigraphy is a technique which is dependent on comparing areas of relative tracer uptake. Generalized small vessel coronary spasm could conceivably result in global hypoperfusion, resulting in a scan in which no single area appears relatively underperfused. This possibility has been postulated to present problems in perfusion scintigraphy in occlusive coronary artery disease, especially disease of the left main coronary artery (17–19). Therefore, we believe that the inability to demonstrate a thallium perfusion defect does not rule out generalized small vessel spasm. In fact, the widespread distribution of ST elevation (I, aVL, V_3 through V_6) during exercise in our patient supports a diffuse ischemic process.

A final possibility is that this case represents a type of small vessel coronary disease unassociated with coronary spasm. The seemingly important role of heart rate in producing the patient's symptoms and the response to beta-receptor blockade suggest that there may be a structural abnormality in the small vessels that produce transmural ischemia and is manifest as ST elevation and chest pain at a certain rate-pressure product. Diffuse small vessel disease could conceivably produce ST segment elevation with normal thallium-201 scintigraphy as a result of similar considerations discussed for small vessel spasm. However, the patient has no evidence of diabetes mellitus or other conditions generally associated with small vessel disease.

Two radionuclide techniques of measuring ventricular function during exercise were employed. On both the first pass and equilibrium studies, the patient exhibited a response to exercise that is not clearly abnormal, but may suggest decreased left ventricular function during exercise and chest pain (20). However, she did not demonstrate frank ST segment elevation during these exercise tests.

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